REMARKS

Claims 14-17, 20-27, 30-33, 63, and 65-68 are pending and rejected. Applicants thank Examiner Kaushal for a personal interview on October 16, 2007, where the outstanding Office Action was discussed.

Claims 30, 63, and 65 have been amended. Claims 69-73 are new.

CLAIM REJECTIONS UNDER 35 U.S.C. §112

Claims 14-17, 20-27, 30-33, 63, and 65-68 are rejected under 35 U.S.C. §112 ¶2 as indefinite. Claim 30 has been amended to properly depend from claim 14. Claim 63 has been amended to properly depend from claim 14. Claim 65 has been amended to recite a bone density pathology and provide proper antecedent basis. New claims 69-73 have been added to recite specific polymorphisms in each of the vitamin D receptor and interleukin-6 (IL-6) genes, to include a control value, and to limit the polymorphism to a single nucleotide polymorphism (SNP).

The Examiner states that claim 65 is "indefinite because it is unclear what encompasses calculating a susceptibility value for the condition by either summing the identified polymorphisms to yield a value for the human, or assigning a weighting factor to each polymorphism and then summing the weighting factors to yield a value for the human".

Applicants respectfully disagree, and have included with this Amendment a Declaration under 37 C.F.R. §1.132 analyzing in detail why the claims are sufficiently definite.

Briefly, Applicants assert that calculating the susceptibility value for the human is disclosed at least at ¶22 and 50-52, using values known to one of ordinary skill in the art. The Declaration asserts that the claims are sufficiently definite in demonstrating how to calculate the susceptibility value by summing, or by assigning a weighting factor and then summing, each polymorphism in each of the vitamin D receptor gene and the IL-6 gene, as Applicants claim.

The Examiner states that "the term "relative degree" in claim 65 is a relative term, which renders the claim indefinite" and that "relative degree" is not defined. Applicants respectfully disagree. The specification discloses a method of assessing the relative susceptibility of a human to an undesirable bone density condition..., and further that "...susceptibility can be calculated relative to a hypothetical human..., alternatively, ... can be calculated relative to another human..." (¶47). Applicants assert that one of ordinary skill in the art would know that "relative degree" represents a comparison of the susceptibility score from the test human, with the susceptibility score of a hypothetical or non-test human, and that the differences in those scores indicate a different relative degree of susceptibility to a bone density disorder. The Declaration also provides support that the term "relative degree" is not indefinite.

The Examiner states that "it is unclear what encompasses 'score correlating polymorphism homozygosity and a bone density associated disorder' " in claim 68. Applicants respectfully disagree. The Declaration describes why such a correlating score is not unclear, and provides a complete analysis of the weighting factor. Briefly, the weighting factor, as described at

¶53, correlates the polymorphism and the bone density associated disorder. The weighting factor is the product of the correlation factor and a constant. However, as also described in ¶53, when the human is homozygous for the polymorphisms, that is, exhibits two copies of the polymorphism, then the weighting factor reflects this situation. Indeed, in calculating the weighting factor, the correlation factor reflects the homozygosity of the polymorphism. Thus, Applicants assert that one of ordinary skill in the art would recognize that if a human is homozygous for a polymorphism that has been correlated with a bone density associated disorder, the presence of two copies of the polymorphism is a factor in determining a susceptibility value for that human.

The Examiner states that "it is unclear what encompasses the product of a constant and a correlation factor", as in claim 26. Applicants respectfully disagree. As described at least at ¶22, the weighting factor, which is summed to provide the susceptibility value, is calculated by multiplying the constant with the correlation factor for that polymorphism. The correlation factor and constant are based on the correlation and relevance, respectively, of the polymorphism with a bone density condition. If the correlation and relevance of the polymorphism and a bone density condition is unknown, a weighting factor of 1.0 is assigned to the polymorphism. If the correlation and the relevance of the polymorphism and a bone density condition are known, then the known values are used as the correlation factor and constant, respectively.

The Examiner states that "it is unclear what are the oligonucleotides encompassing disorder associated polymorphism and non-disorder associated polymorphism". Applicants respectfully disagree. One of ordinary skill in the art knows that polymorphisms, particularly single nucleotide polymorphisms (SNPs), are alternative nucleotides at a specific position of a nucleic acid, in this case, the gene encoding each of the vitamin D receptor and IL-6. In some cases, a particular nucleotide at a SNP is associated with a bone density condition; in other cases it is not. Thus, an oligonucleotide that specifically recognizes the sequence comprising the disorder associated polymorphism will anneal to the disorder associated sequence with higher stringency than it will anneal to the non-disorder associated polymorphism sequence.

For at least the reasons described above and in the accompanying Declaration, Applicants respectfully assert that claims 14-17, 20-27, 30-33, 63, and 65-68 are sufficiently definite, and respectfully request withdrawal of the rejection.

Claims 14-17, 20-27, 30-33, 63, and 65-68 are rejected under 35 U.S.C. §112 ¶1 as not described and enabled.

The Examiner states that the "specification fails to disclose any variants of gene encoding vitamin D receptor and interleukin-6 which one skilled in the art would use to practice the invention". Applicants respectfully assert that one of ordinary skill in the art, without undue experimentation, can readily determine variants of the human vitamin D receptor gene and IL-6

gene. As only one example, with other examples provided in the Declaration, a search of the literature by one of ordinary skill in the art at the time the invention was made would have found, for example, Miyamoto et al., Structural Organization of the Human Vitamin D Receptor Chromosomal Gene and Its Promoter, Mol. Endocrinol. 11, 1165-1179 (1997); and Baker et al., Cloning and Expression of Full-Length cDNA Encoding Human Vitamin D Receptor, Proc. Natl. Acad. Sci. 85, 3294-3298 (1988), where he/she can readily determine that there are four splice variants of the human vitamin D receptor gene. Applicant has also added claim 71 which recites specific polymorphisms in each of a gene encoding IL-6 and a gene encoding vitamin D receptor, with support found at least in the prior art, for example, Ferrari, et al., A Functional Polymorphic Variant in the Interleukin-6 Gene Promoter Associated with Low Bone Resorption in Postmenopausal Women, Arthritis Rheum. 44, 196-201 (2001)(cited in the specification); and Gennari et al., Vitamin D and Estrogen Receptor Allelic Variants in Italian Postmenopausal Women: Evidence of Multiple Gene Contributing to Bone Mineral Density, J. Clin. Endocrinol. Metab. 83, 939-944 (1998), respectively (Exhibits attached).

The Examiner states that the specification fails to disclose "first and second oligonucleotides especially in context of any and all variants encoding vitamin D receptor and interleukin-6". As analyzed above and described in the Declaration, Applicants assert that the sequence of each of the vitamin D receptor gene and IL-6 gene, and their bone density associated polymorphisms, are readily obtainable, for example, in the literature at the time of the invention. As also analyzed above, the sequence of the first and second oligonucleotides are complimentary to the gene sequence comprising the polymorphism of interest. Thus, Applicants assert that the first and second oligonucleotides are known to one of ordinary skill in the art based on the known gene and polymorphism sequences.

The Examiner also states that the specification "fails to disclose representative number of species by structure and function encompassed by genus as claimed". Applicants respectfully disagree. The specification at p. 15 describes a bone density associated polymorphism in each of the human vitamin D receptor gene and the IL-6 gene. Further, as analyzed above and in the Declaration, one of ordinary skill in the art can readily recognize a first and second oligonucleotide based on this information. Additional bone density associated polymorphisms in these two genes are known in the art, and thus one of ordinary skill in the art can determine a first and second oligonucleotide based on this information.

The Examiner states that the specification fails to disclose "... any variants of gene encoding vitamin D receptor and interleukin-6 ...", and "... make and use any set of first and second oligonucleotides especially in context of any and all variants of gene encoding vitamin D receptor and interleukin-6 and associated disorders...". Applicants respectfully disagree. As analyzed above and in the Declaration, variants of the vitamin D receptor gene and IL-6 gene,

and making and using first and second oligonucleotides are readily known to one of ordinary skill in the art.

The Examiner states that "Applicant fails to consider that the demonstration of an association between a candidate gene and BMD does not necessarily mean that the gene is causally responsible for the effect observed". Applicants respectfully assert that the problem in associating a phenotype with a genotype is well known to one of ordinary skill in the art. However, as detailed in the Declaration, not only is the problem known in the art, but methods and techniques for addressing the problem are known in the art. Thus, Applicants respectfully assert that the association between the polymorphism and the bone density condition can be established.

The Examiner states that the burden shifts to Applicants to establish that one skilled in the art would be able to practice the invention. The accompanying Declaration provides detailed analysis and evidence that one skilled in the art would be able to do so. For example, it provides examples of determining bone density associated polymorphisms, gene variants, first and second oligonucleotides, weighting factor, and susceptibility values. Applicants also provide evidence in Appendix A of the Declaration that their method does not require "ingenuity beyond that to be expected of one of ordinary skill in the art", but requires knowledge of one of ordinary skill in the art and that any experimentation would not be undue.

For at least these reasons, Applicants respectfully assert that claims 14-17, 20-27, 30-33, 63, and 65-68 are enabled and described by the specification and respectfully request withdrawal of the rejection.

CONCLUSION

The application is believed to be in complete condition for allowance. The fee for a one-month extension of $120.00 to respond is authorized to be charged to credit card (see Electronic Free Calculation sheet). No other fees are believed due but, if deemed necessary, may be charged to Deposit Account No. 20-0809. The Examiner is invited to contact Applicant's undersigned representative with questions.

Respectfully submitted,

/Beverly A. Lyman/
Beverly A. Lyman, Ph.D.
Reg. No. 41,961

Thompson Hine, LLP
312 Walnut Street
14th Floor
Cincinnati OH 45202
Direct Dial 513 352 6596

664406